Challenges to Translation and the Hippocratic Oath by Premature Termination of Spinal Cord Stem Cell-Based Trials

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VIEWPOINT

Challenges to Translation and the Hippocratic Oath by Premature Termination of Spinal Cord Stem Cell–Based Trials

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Untimely termination of clinical trials owing to strategic corporate considerations (30%)[1] or futility analysis (50%)[1] account for most prematurely discontinued studies, and spinal cord injury (SCI) trials are no exception (**Figure**).[2] In this commentary, we advocate for clear termination rules, including an orderly exit plan, as a prerequisite for regulatory approval to optimize safe and effective clinical translation. Invasive cell transplant trials in SCI require excellent preclinical and clinical safety and efficacy data, pioneering spirit, and intensive resource investment. However, premature termination without an orderly exit plan produces harmful consequences worthy of discussion.

The Proneuron Phase 2 Autologous Incubated Macrophage Study was suspended owing to business considerations after 50 of 61 patients with complete paralysis (C5 motor/C4 sensory –T11) were randomized between 2003 and 2009 (1816 prescreened and screened).[2] The company website indicated that clinical follow-up was intended for patients already enrolled in the study, but confirmation could not be found either through website updates or subsequent publications.

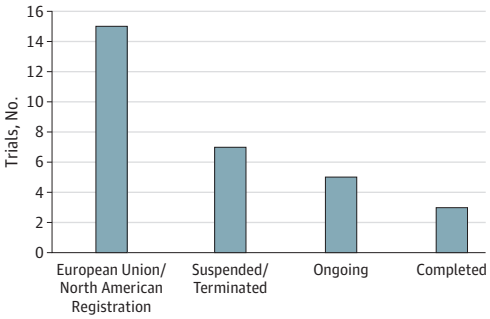
The Geron Phase 1 Study of GRNOPC1 (human embryonic stem cell–derived oligodendrocyte progenitors) introduced stem cell transplantation in patients with complete lower-body paralysis within 7 to 14 days post-SCI with enormous publicity but enrolled only 5 of 10 patients over 11 months before prematurely terminating the study in 2011. Within the last 6 months, 2 trials to prematurely terminate were the Stem Cells Inc Human Central Nervous System Stem Cells Phase 2 Study in cervical SCI and the consecutive Long-Term Follow-Up Study investigating human, fetal-derived neural stem cells in thoracic SCI.[3] Both studies were halted at midterm, although a phase 1/2a study in thoracic SCI (n = 12) was successfully completed. No reports of post-termination follow-up were found. The aftermath of these discontinued stem cell trials may be a deterrent toward (1) new investments into scientifically sound trials and (2) equipoise for ongoing stem cell tourism toward unproven treatments.[4]

Regulatory approval of trials depends on detailed evaluation of the risk-benefit relationship for the patient. Subsequent protocol changes initiated by any party may not shift the risk-benefit relationship to less than favorable. Premature study termination jeopardizes acquisition of knowledge. This in turn affects the benefit-risk ratio, which was calculated initially based on the assumption that the study would deliver on the task of optimal knowledge gain in a new frontier of research.

On the other hand, industry sponsors, taking up the challenge of translational research and early therapeutic development, inevitably need to have some means to deviate from original plans while also responding to vital business considerations. This is made possible if companies can rely on the opportunity to unilaterally decide for early termination or even corporate dissolution. To restrict sponsors' ability to enforce such management decisions[5] would likely have a negative long-term effect on interventional trials, with further lowered appeal to invest in an orphan-like condition (eg, SCI), resulting in impeded translation of new therapies.

Sponsors often depend on futility analyses to test the ability of a trial to achieve its objectives (ie, effectiveness) in consideration of early termination (or not).[6] However, applied to early phase 1/2a trials, the validity of a futility analysis is compromised by insufficient statistical power, sometimes lower than the predictive power of a coin toss (50%) to detect even large effects. Early and underpowered futility decisions also abrogate the precious opportunity to address important secondary research questions (ie, patient stratification and secondary efficacy measures) that provide additional disease

Figure. 2003-2016 European Union and North American Cell-Based Clinical Trials Registered With clinicaltrials.gov



Suspended/terminated trials predominate the field of spinal cord injury stem cell transplantation (n = 7 of 15) in North America and Europe and pose the question on how academia and the pharmaceutical industry can work together more effectively. The provision of an exit plan covering the follow-up examinations of all patients enrolled until the termination date needs to be made obligatory for trial approval. Translation of basic and preclinical stem cell research efforts will be even more difficult in the future given the premature termination of prominent spinal cord injury early-phase trials owing to futility analysis underpowered to reveal efficacy. Discontinued stem cell trials in spinal cord injury demarcate an interim burial mound located in the "valley of death" spanning from basic/preclinical to clinical research and neglects the opportunity to improve the conduct of future stem cell studies through investigation of secondary end points.

and/or therapy insights. Decisions to discontinue therapeutic exposure if there are adverse effects with no benefits or subtle benefits outweighed by harm should be the responsibility of a data safety monitoring board independent from futility analysis or strategic decisions.

When a well-justified decision to terminate a clinical research study is reached,[5,7] it is imperative that the sponsor (corporate, governmental, or university) continues to ensure follow-up clinical evaluations for all participants who have entered the trial. Abandoned follow-up (1) ultimately results in "poor science" (eg, incomplete data sets) and (2) harms the doctor-researcher/patient relationship. Requiring sponsors to guarantee sufficient funds upfront to safeguard follow-up for each patient can negate this.

As the International Council for Harmonization remains silent on the financial responsibility of sponsors to provide follow-up after early termination of a trial, we advocate for the linkage of approval of future trials by regulatory authorities with an a priori orderly exit strategy. Clinical investigators remain bound by the Hippocratic Oath, which orders physicians to keep patients from harm and injustice even if their institution is unable or unwilling to bear the costs of early termination of sponsored trials. In the case of the early termination of Stem Cells Inc Human Central Nervous System Stem Cells Phase 2 cervical trial, no resources were provided for a final study termination visit, even in patients who were just a few weeks post–cell transplantation.

Premature termination of a clinical trial without an orderly closure plan is a threat to the trust of patient volunteers and clinical investigators who feel bound to their patients and by the Hippocratic Oath. Discussions with regulatory agencies are warranted to ensure that the financial and ethical burden of early termination is appropriately balanced to ensure the well-being of patient volunteers.

ARTICLE INFORMATION

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